Chemical Prioritization and Profiling Applications of ToxPi for Tox21 Data

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Abstract

The Toxicological Prioritization Index (ToxPi™) framework was developed as a decision-support tool to aid in the rational prioritization of chemicals for integrated toxicity testing. ToxPi consolidates information from multiple domains—including ToxCast™ *in vitro* bioactivity profiles (a wide-ranging battery of over 500 high-throughput screening assays), inferred toxicity pathways, exposure predictions, and chemical properties/descriptors—into comprehensive toxicity scores and multivariate visualizations representing the contribution of each data domain to overall priority rankings. Here, we demonstrate applications of ToxPi that integrate data from across the Tox21 partnership. These include an application for endocrine activity, an application that simultaneously considers four sectors of toxicological concern (systemic, cancer, developmental, and reproductive), and an application that foresees how ToxPi could be used for assigning future test chemicals to toxicological activity "neighborhoods". Taken together, these applications demonstrate the utility of this framework for communicating results of the high-dimensional data generated as part of Tox21 and supporting decisions on targeted testing needs. *This abstract does not necessarily reflect U.S. EPA policy.*

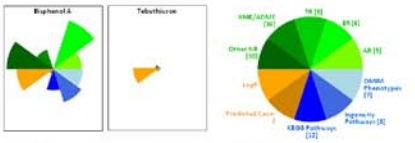
Application 1: Endocrine Activity

1.1: Define ToxPi for endocrine activity

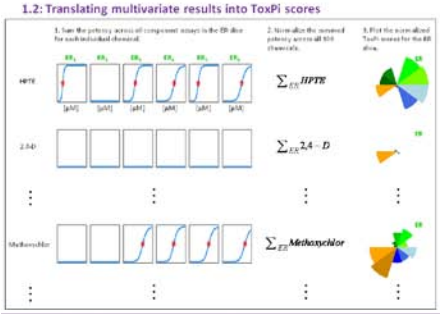
Each chemical signature/profile gives a **Tox**icological **P**riority **I**ndex (**ToxPi**) score that is useful for ranking chemicals

$$\text{ToxPi} = \sum_i^n \mathbf{w}_i * \mathbf{assay}_i + \sum_j^m \mathbf{w}_j * \mathbf{chemProp}_j + \sum_p^o \mathbf{w}_p * \mathbf{pathway}_p$$

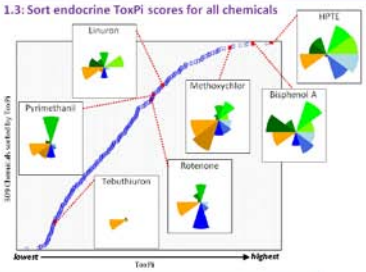
ToxPi = f(In vitro assays + Chemical properties + Pathways)



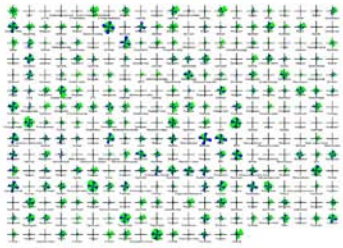
1.2: Translating multivariate results into ToxPi scores



1.3: Sort endocrine ToxPi scores for all chemicals



2.4: Calculate multi-sector ToxPi scores for all chemicals



Application 2: Multiple Sectors of Toxicological Concern

2.1: Organize *in vivo* endpoints into four sectors

The *in vivo* endpoints from studies captured in ToxRefDB (see Martin et al. 2009) that had at least one statistically significant association with *in vitro* ToxCast assays were organized into four sectors of toxicological relevance. The Cancer (CANCER=C) sector included endpoints such as neoplastic lesions and tumors. The Developmental (DEVEL=D) sector included endpoints such as cleft palate and skeletal abnormalities. The Reproductive (REPRO=R) sector included endpoints such as litter size and offspring survival. The Systemic (SYSTEMIC=C) sector included endpoints such as non-cancer lesions to specific organs and systemic outcomes not specified in another sector.

2.2: Organize *in vitro* assays and pathways associated with each sector of *in vivo* endpoints

ToxCast assay results (AC_{50} values) and pathway perturbation scores (see Judson et al. 2010) were mapped to sectors if there was a significant statistical association between an assay/pathway and an *in vivo* endpoint for that sector.

2.3: Define the ToxPi as a function of the data identified above

The ToxPi is a weighted sum of components across all sectors $\{C,D,R,S\} \in S$

$$\text{ToxPi} = \sum_s^S \left(\sum_i^{A_s} \mathbf{w}_{i,s} * \mathbf{assay}_{i,s} + \sum_j^{P_s} \mathbf{w}_{p_j} * \mathbf{pathway}_{p_j} \right)$$

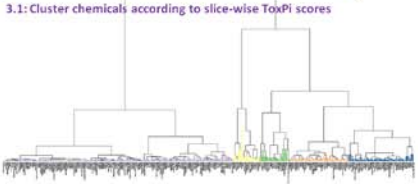
ToxPi = f(In vitro assays + Pathways)

ToxPi terminology:

Sector: area of toxicological concern (in this case, one of four: Cancer, Developmental, Reproductive, Systemic)
Domains: basic data types represented by slices of a given color family (in vitro assay slices in shades of green, pathways in blue, etc.)
Slices: represent data from related assays, chemical properties or pathways
Components: data from individual assays, chemical properties or pathways

Application 3: Predictive Binning to Support Targeted Testing

3.1: Cluster chemicals according to slice-wise ToxPi scores



3.2: Calculate ToxPi on new "test" chemicals {X, Y, Z}

ToxPi(X) = ToxPi(Y) = ToxPi(Z) =

3.3: Assign "test" chemicals to existing cluster bins (neighborhoods) defined in Section 3.1 to support targeted testing decisions

References

Reif et al. (2010) Endocrine Profiling and Prioritization of Environmental Chemicals Using ToxCast Data *Environmental Health Perspectives*

Judson et al. (2010) In Vitro Screening of Environmental Chemicals for Targeted Testing Prioritization - The ToxCast Project *Environmental Health Perspectives*

Martin et al. (2009) Profiling Chemicals Based on Chronic Toxicity Results from the U.S. EPA ToxRef Database *Environmental Health Perspectives*